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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/737,208	12/16/2003	Stephen D. Gillies	LEX-023	6855

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EXAMINER	
GALVEZ, JAMES JASON	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/737,208	GILLIES ET AL.	
	Examiner	Art Unit	
	J. Jason Galvez	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14-24 and 27-44* is/are pending in the application.

4a) Of the above claim(s) *20-22 and 27-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14-19,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group 1 and the species of cytokines, an interleukin, in the reply filed on 3/15/2005 is acknowledged. Claims 12-13 and 25-26 are cancelled. Claims 1-11, 14-24, and, new claims, 27-44 are pending. Claims 20-22 are drawn to non-elected species while 14-15 and 27-44 (new claims) are drawn to non-elected subject matter. Accordingly, claims 1-11, 16-19, and 23-24 are under examination.

Drawings

Applicant is advised that upon issuance of a patent, the complete text of the sequence listing submitted in compliance with 37 C.F.R.§§1.821-1.825 will be published as part of the patent. Therefore, it is redundant to repeat the sequence information in the form of a Figure(s), see Fig. 2 A-G and Fig. 3 A-B. Applicant should amend the specification to delete any Figure(s) consisting only of nucleic acid or protein sequences that have been submitted in its entirety in computer readable format (i.e. as SEQ ID NOs.) and should further amend the specification to reflect the replacement of the Figure(s) by the appropriate SEQ ID NO:.

Specification

The abstract of the disclosure is objected to because it contains irrelevant text in the form of numbers, "2722168". Correction is required. See MPEP § 608.01(b).

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the Examiner has cited the reference on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 16-19, and 23-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti-GD2 antibody comprising both light chain and heavy chain variable regions and fusion protein comprising an anti-GD2 antibody also comprising both light chain and heavy chain variable regions and a 1^{st} or a 1^{st} and a 2^{nd} moiety consisting of IL-2 and/or IL-12 that targets cancer cells delivering IL-2 and/or IL-12 to said cancer cells, does not reasonably provide enablement for anti-GD2 antibody variable regions or fragments and a fusion protein comprising an anti-GD2 antibody comprising a light chain or a heavy chain variable region singularly and a 1^{st} or a 1^{st} and a 2^{nd} moiety comprising a non-immunoglobulin molecule that targets cancer cells delivering non-immunoglobulin molecules to said

cancer cells. Furthermore, the instant specification also does not provide enablement for antibody variable regions (SEQ ID NO: 1 and 2), antibodies comprising said variable regions, or fusion proteins comprising said variable regions or said antibodies wherein the molecule is less immunogenic than a variable region of a mouse anti-GD2 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the 1) quantity of experimentation necessary, 2) amount of direction or guidance presented, 3) presence or absence of working examples, 4) nature of the invention, 5) state of the prior art, 6) relative skill of those in the art, 7) predictability or unpredictability of the art, and 8) breath of claims. *Ex Parte Forman*, (230 USPQ 546 (Bd. Pat. App. & Int. 1986)); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1-11, 16-19, and 23-24 are drawn to antibody variable regions (SEQ ID NO: 1 and 2), antibodies comprising said variable regions, or fusion proteins comprising said variable regions or said antibodies wherein the molecule is less immunogenic than a variable region of a mouse anti-GD2 antibody. However, Applicant has not established that any of the molecules encompassed by the instant invention contains any molecules that are less immunogenic than a variable region of a mouse anti-GD2 antibody. Merely stating properties is not sufficient to enable the instant invention. Furthermore, since there are no specific teachings of sites and/or substitutions

regarding the humanization of mouse anti-GD2 antibodies that actually result in a less immunogenic variable region, antibody, or fusion protein of the instant invention it would not be possible to know how to make the claimed invention. Accordingly, a person of ordinary skill in the art would not know how to make and/or use the instant invention because it is not known, based in the instant specification, if the molecules encompassed by the claims are less immunogenic than a variable region of a mouse anti-GD2 antibody.

Claims 1-2, 6-11, 16-19, and 23-24 are drawn to an anti-GD2 antibody variable region, fragments of variable regions, *e.g.* amino acids 1-23 of SEQ ID NO: 1, and fusion proteins comprising said antibody variable regions comprising a light chain or a heavy chain variable region. The claims currently read on using only portions of the antigen-binding domain. Alberts *et al.* teach the antigen-binding domain is made up of the light chain and heavy chain variable regions (*The Cell* 2002, Garland Science, 4th edition, esp. p. 161: Figure 3-42.). Furthermore, do Couto *et al.* teach, both the light chain and heavy chain variable regions are generally required for the binding properties of the antibody (US Patent No. 6,309,636 B1; filing date: 9/1995; see column 7: lines 32-34). Therefore, since Applicant has provided no data or rationale supporting the claims drawn to portions of the antigen-binding domain a person of ordinary skill in the art would not know how to use the invention commensurate in scope with the claims. For example, would a fusion protein comprising only amino acids 1-23 of SEQ ID NO: 1 and IL-2 function within the framework of the present invention, *i.e.* would a portion of the light chain variable region confer binding affinity suitable to deliver IL-2 to cancer

cells? Without at least a representative set of fusion proteins comprising only a portion of the antigen-binding domain it would not be possible to predict whether said fusion proteins would function properly.

Claims 6, 16, and 23 are drawn to a fusion protein comprising an anti-GD2 antibody and a 1st or a 1st and a 2nd moiety comprising a non-immunoglobulin molecule. The claims currently read on fusion proteins comprising any non-immunoglobulin molecule, such as glucose. As such a person of ordinary skill in the art would not know how to use the instant invention. For example, would fusion proteins consisting of glucose at the 1st and/or 2nd moiety have the desired effect, which has been interpreted to be the delivery of cytotoxic molecules to cancer cells? There is no indication in the specification or the relevant art that would indicate a fusion protein comprising any non-immunoglobulin molecule, introduced as a 1st or a 1st and a 2nd moiety, would be able to be used and still function properly within the context of the instant invention.

Claims 1-11, 16-19, and 23-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The factors to be considered when determining if the disclosure satisfies written description requirements include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof.

Claims 1-11, 16-19, and 23-24 are drawn to antibody variable regions (SEQ ID NO: 1 and 2), antibodies comprising said variable regions, or fusion proteins comprising said variable regions or said antibodies wherein the molecule is less immunogenic than a variable region of a mouse anti-GD2 antibody. However, Applicant has not established that any of the molecules encompassed by the instant invention contains any molecules that are less immunogenic than a variable region of a mouse anti-GD2 antibody. Applicant has not set forth any evidence confirming the molecules of the instant invention are less immunogenic than a variable region of a mouse anti-GD2 antibody. Therefore, the instant specification does not reasonably convey to a person of ordinary skill in the art that Applicant had possession of the claimed invention at the time of filing because it is not known if all the molecules of the instant invention are less immunogenic than a variable region of a mouse anti-GD2 antibody.

Claims 6, 16, and 23 are drawn to a fusion protein comprising a 1st or a 1st and a 2nd moiety comprising a non-immunoglobulin molecule. The claims currently read on a fusion protein comprising any non-immunoglobulin molecule including glucose and interleukins. The specification in no way limits what the moiety comprising a non-immunoglobulin molecule could encompass, which makes the fusion protein drawn a genus of fusion proteins. Furthermore, Applicant has not described the common structural and/or functional characteristics of the moiety comprising the non-immunoglobulin molecule. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. Accordingly, in the absence of sufficient recitation of

distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states: "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, a person of ordinary skill in the art cannot envision the detailed chemical structure of the encompassed genus of fusion proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only fusion protein comprising anti-GD2 antibodies and IL-2 and/or IL-12, but not the full breadth of the claim meets the written description provision of 35

U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-11 and 16-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Lode *et al.* (J Clin Invest. 2000, Vol. 105(11): pp. 1623-1630). Lode *et al.* teach a humanized anti-GD2 immunocytokine designated hu14.18-IL-2 (p. 1624: column 1, paragraph 3). Applicant discloses the present invention as comprising sequences of the variable light chain and variable heavy chain regions of hu14.18 and fusion proteins comprising cytokines such as IL-2 (pp. 6-7: [00023] – [00029]; p. 12: [00045]). Thus, even though Load *et al.* do not specifically disclose the sequence of hu14.18-IL-2 it comprises, absent any evidence to the contrary, the sequences of SEQ ID NO: 1, SEQ ID NO: 2, and fusion proteins of the instant invention comprising IL-2 because SEQ ID

NO: 1 and SEQ ID NO: 2 are disclosed as the variable light chain and variable heavy chain regions of hu14.18. Therefore, Load *et al.* teach an anti-GD2 antibody designated hu14.18 and a fusion proteins comprising said antibody and IL-2, meeting the limitations of the claims.

Claims 1-11 and 16-19 are also rejected under 35 U.S.C. 102(e) as being anticipated by Gillies *et al.* (US 2003/0166877 A1; effective filing date: 3/29/2002). Gillies *et al.* disclosed a fusion protein designated as hu14.18-IL-2. For the reasons previously set forth for the claims being anticipated by Load *et al.* the claims are also rejected by Gillies *et al.* since Gillies *et al.* also disclose hu14-18-IL-2. Thus, Gillies *et al.* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lode *et al.* (J Clin Invest. 2000, Vol. 105(11): pp. 1623-1630) as applied to claims 1-11 and 16-19 above, and further in view of Gillies *et al.* (WO 01/10912 A1; publication date: 2/15/2001). Load *et al.* teach sequences comprising regions, antibodies, and fusion proteins comprising IL-2 of the instant invention, as set forth above. However, Load *et al.* do not teach fusion proteins comprising a second moiety comprising a non-immunoglobulin wherein said non-immunoglobulin is IL-2 or IL-12.

Gillies *et al.* teach optimum immune responses can be achieved by using different cytokines, particularly directing examples to IL-2 and IL-12 (p. 1: lines 20-24). Gillies *et al.* further teach antibodies comprising IL-12 and IL-2 (p. 7: lines 14-20). Thus, Gillies *et al.* teach multiple cytokines are needed to elicit optimal immune responses and antibodies comprising a first and a second moiety consisting of IL-12 and IL-2.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to make antibodies disclosed by Load *et al.* further comprising a second non-immunoglobulin moiety as taught by Gillies *et al.* Additionally, a person of ordinary skill in the art would have been motivated to make an antibody comprising two non-immunoglobulin moieties because Gillies *et al.* teach optimum immune responses can be attained by using more than one cytokine. Furthermore, following the same logic, it would be obvious to make antibodies comprising any two non-immunoglobulin molecules that have been shown to act synergistically. Finally, the expectation of success is reasonably assured based on teachings set forth by Gillies *et al.* where it is taught how to make antibodies comprising multiple non-immunoglobulin moieties.

Double Patenting

Claims 6, 16-19, and 23-24 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-5 and 13 of copending Application No. 11/040,071. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: both copending applications are claiming proteins, including fusion proteins, that are not patentably distinct from one another. Claims 1-5 and 13 of copending application '791 encompass proteins, including fusion proteins, comprising anti-GD2 antibody variable regions, which is encompasses the claims of 6, 16-19, and 23-24 of the instant application where fusion protein comprising anti-GD2 antibody variable regions, SEQ ID NO: 1 and SEQ ID NO: 2, are being claimed. Additionally, the heavy chain variable region recited in claim 13, as SEQ ID NO: 1, is identical to the heavy chain variable region of SEQ ID NO: 2 recited in claim 6 of the instant application.

Furthermore, there is no apparent reason why Applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application.

Conclusion

NO CLAIMS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **J. Jason Galvez, Ph.D**. whose telephone number is **571-272-2935**. The examiner can normally be reached Monday through Friday 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback, Ph.D.** can be reached at **571-272-0887**.

The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JANET ANDRES
PRIMARY EXAMINER

JJG
5/20/2005